

Acetaminophen Toxicity: Changing Perceptions on a Social/Medical Issue

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Acetaminophen overdoses are the leading cause of acute liver failure (ALF) in the United States, Great Britain and most of Europe. Acetaminophen toxicity accounts for approximately 50% of all cases of ALF in the United States and carries a 30% mortality.¹ More than 100,000 calls to Poison Control Centers, 56,000 emergency room visits, 2,600 hospitalizations and nearly 500 deaths are attributed to acetaminophen in this country annually.² The incidence of acetaminophen-related ALF exceeds by at least three-fold that due to all other idiosyncratic drug reactions combined.³ Nevertheless, acetaminophen has been a highly successful product. Off patent long ago, it is found in more than 300 products with sales in the billions of dollars annually. A combined preparation consisting of acetaminophen together with a narcotic is the top selling generic drug in the United States, with 109 million prescriptions written in 2006.⁴ The Public Policy Committee of the American Association for the Study of Liver Diseases (AASLD) began a year ago to look into what might be done to address this unfavorable health issue. I was asked by the Committee to write this commentary as a brief overview of acetaminophen toxicity and to discuss possible ways to bring about harm reduction by beginning to partner with regulatory agencies to alter the way acetaminophen is marketed and sold in the United States.

Clinical Background

Acetaminophen has been available since the 1950s as an over-the-counter product for pain and fever relief. First

marketed in 1955 in the United States as Tylenol®, and in 1956 in the United Kingdom as Panadol®, acetaminophen has long been recognized as potentially lethal because of dose-related hepatic, and often renal, injury.^{5,6} Although its metabolism is quite well understood, the mechanism of acetaminophen toxicity remains somewhat a mystery with recent evidence suggesting that multiple cytotoxic pathways are involved.⁷ Historically, alcohol use was claimed as an important risk factor, with the accidental nature of acetaminophen toxicity in alcoholics being termed a ‘therapeutic misadventure.’^{8,9} Metabolic synergy between alcohol and acetaminophen appears to enhance the toxic reaction but how important this is clinically remains a matter of debate.^{10,11} Low dose ingestions having harmful consequences appear to be more likely in association with alcohol use.¹² Prior to the 1990s, only a few cases of acetaminophen poisoning had been reported; acetaminophen toxicity was not listed at all in transplant series until two reports in the late 1990’s. The Acute Liver Failure Study Group has compiled data on more than 500 acetaminophen-related ALF cases showing that the number of cases has increased considerably since 1998 (Fig. 1).¹² Suicidal overdose of acetaminophen is the most frequent form of liver injury in the United Kingdom while unintentional cases occur more commonly in the United States.¹³ In a study of a U.S. inner city hospital admissions, suicidal acetaminophen cases exceeded unintentional ones by more than nearly three-fold, but were much less likely to be fatal or to be associated with alcohol. Most people who attempt suicide admit to the misdeed and seek help early, and are then able to receive the anti-

Abbreviations: ALF, acute liver failure; AASLD, American Association for the Study of Liver Diseases; FDA, U.S. Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug; NDAC, non-prescription drug advisory committee; OTC, over-the-counter; PDP, product display panel.

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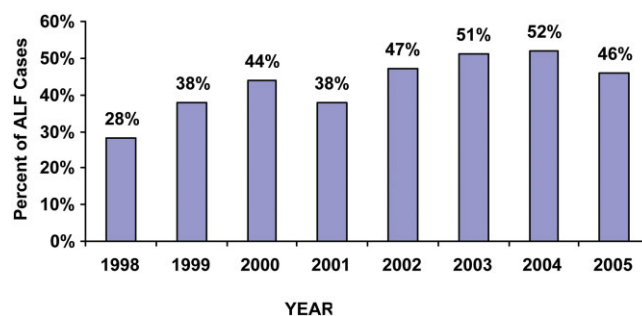


Fig. 1. Proportion of ALF cases attributed to acetaminophen between January 1998 and December 2005 (ALF Study Group, unpublished data).

dote N-acetylcysteine in a timely fashion, usually within 12 hours. Unintentional cases of overdose present themselves late after multiple smaller but excessive doses over three or more days. They typically do not recognize that anything harmful has occurred, only that they are becoming ill. The number of cases where the dose of acetaminophen does not exceed the amount recommended in the package labeling is uncertain, but probably represents 10% of those reaching ALF. Median values for both types average 20 grams. In the ALF Study Group analysis, roughly half were due to intentional self-harm and half were unintentional. Most unintentional overdose patients repeatedly exceed the package labeling limits of 4 grams. This group used narcotic-acetaminophen combinations frequently (62% of the time), many taking up to 20 or more tablets daily, which would constitute 10 gm acetaminophen in a single-tablet combination such as hydrocodone 5mg/acetaminophen 500mg. While tolerance to acetaminophen probably does occur when the dose is gradually increased, continued increases presumably exceed a threshold, resulting in toxicity that is similar in severity and acuity to single time point overdoses.¹⁴ Thirty-eight percent had taken more than one acetaminophen-containing agent simultaneously. Positive toxicology screening tests for marijuana, cocaine or alcohol were common in this group. Thus, the unintentional group is of particular interest; they lack any understanding of risk associated with acetaminophen or any awareness of what products contain it, frequently suffer from chronic pain and depression and may be involved in other high-risk behaviors.

Regulatory History

Acetaminophen was approved by the U.S. Food and Drug Administration (FDA) in 1955 in a 325 mg size (before the legislative requirement enacted in 1962 that new drugs had to be shown to be safe and effective). It only became widely used in the fallout from the discovery in the 1980s that Reye's syndrome (encephalopathy with liver failure related to mitochondrial dysfunction) appeared to be associated with aspirin ingestion for treatment of symptoms of viral respiratory infections. Although this syndrome is essentially limited to children, aspirin became thought of as highly risky for this reason and thus acetaminophen was the natural replacement, marketed effectively under the brand name Tylenol®. Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, but also ibuprofen and many others have, to a greater or lesser extent, issues related to ulcer formation, gastrointestinal bleeding, some idiosyncratic hepatic toxicity, nephrotoxicity and, more recently, cardiac ischemic events. Acetaminophen does not share these attributes,



Fig. 2. "Safest." Coupon received by the author upon filling a prescription for a 'statin'. Despite concerns over statin toxicity, more patients die of acetaminophen poisoning in one year than can be attributed to all the statins combined over all the years that these drugs have been in use.

another reason that it may appear to be the safer choice. Indeed, recent advertisements have touted the drug as "safest," a claim most hepatologists might dispute (Fig. 2). To date, package labeling for acetaminophen has never fully disclosed that acetaminophen causes liver *failure*, usually cautioning drinkers to consult their doctor if consuming the product *and* three or more alcoholic drinks. I often try to imagine the likelihood of an alcoholic dialing his physician at 3 AM to discuss the risk/benefit ratio of acetaminophen prior to downing two Tylenols (or some Nyquil®) for that hangover and what his physician might say if he did.

Because of the concerns raised by the ALF Study Group and other data, the FDA held a two-day meeting of its non-prescription drug advisory committee (NDAC) in September 2002 to consider two issues: acetaminophen hepatotoxicity and gastrointestinal bleeding and nephrotoxicity associated with the NSAIDs.² The NDAC was tasked by FDA to only consider revision of package labeling for acetaminophen, and was not invited to review any other restrictions on its use or distribution. The ALF Study Group findings were presented and reviewed. During the public comment period a study performed by pharmacists at the University of Pennsylvania demonstrated similar findings to the ALF Study Group data.^{2,14} The committee voted unanimously to recommend "immediate" changes to package labeling, leaving the details to FDA but specifying that all compounds include the generic name acetaminophen on the front of the package in a reasonable size font, that greater efforts directed toward patient education be undertaken and that the wording relating to alcohol in the precaution section be revised.

The recommendations were finally put forward as a Proposed Amendment of the Tentative Final Monograph; Required Warnings and Other Labeling, in December 2006 more than 4 years later.¹⁵ Public comment was requested and AASLD has replied in detail (see full documents on AASLD website: www.aasld.org).

The proposals in the 147-page FDA document, as expected, were limited to changing the package label and considering an education program for patients and physicians. It was decided that not enough data existed to consider lowering the maximum daily safe dose. Limiting package size or introducing blister packing (both in place in the United Kingdom since 1998) were not discussed at the NDAC meeting, nor was unbundling of narcotic compounds containing acetaminophen considered. Suicidal ingestions were barely touched upon during the meeting, despite the fact that they cause a similar number of fatalities to unintentional cases and, in terms of overall numbers, exceed unintentional hospitalizations by threefold. Improving education and labeling might help decrease use of multiple preparations and perhaps make individuals more mindful that acetaminophen can cause serious liver injury. Current package labeling is woefully inadequate both in placement and content; the new Proposed Amendment will begin to deal with this. However, the amount of tablets that can be purchased or improvement in the packaging itself has not been addressed: acetaminophen remains on the U.S. market in bottles of as many as 500 tablets containing 500 mg each, enough to kill 10-20 people.

The British Experience

Paracetamol, as acetaminophen is known abroad, accounts for 200-500 deaths and 20-40 liver transplants annually in the United Kingdom alone.^{16,17} More than 80% are deemed to be suicides and unintentional cases are less often observed than in the United States. An abrupt increase in the cases due to paracetamol occurred in the mid-1990s with 37,000 hospitalizations and 562 deaths in England and Wales in 1997, considerably higher than the comparable numbers for 1995.¹⁸ Based on the high number of suicidal overdoses that occur in the United Kingdom, Parliament enacted laws in 1998 that limited package size and brought in blister packaging. Restricting availability of large quantities in the home was the goal of the legislation. Thus, package size was restricted to 16 in general stores and 24 in pharmacies, with larger quantities available by prescription or at the discretion of the pharmacist. In addition, blister packaging was used presumably to limit impulsive overdosing or at least to make it a bit harder.

In the years since the legislation went into effect the number of hospital admissions for acetaminophen overdoses decreased by 27% while the number of ICU admissions at Kings College Hospital where there is a dedicated intensive care program in liver failure, declined from 119 in 1998 to 25-40 during the period 2002-2005 (W. Bernal, unpublished data). Other figures suggest at least a one third decline in admissions, listings for transplantation and transplants at most of the UK transplant centers.^{18,19} A similar decline in Scotland was not observed for unclear reasons.²⁰ Sales in the meantime had increased to pre-legislation values, and compliance with the law may have become a problem, since clerks currently do not uniformly enforce the one package at a time rule implied by the smaller size packages.²¹ A recent study has suggested that the decline in paracetamol-related incidents coincided with a decline in all forms of suicidal events in Britain that may have had been the result of other larger social changes such as a decline in unemployment, and not the legislation itself.²²

Current U.S. Options

Given the present circumstances and the publication of the Proposed Amendment in December, the AASLD has now developed a detailed response. The FDA will begin to implement the changes planned (presumably with modifications, based on public comment). The AASLD response is paraphrased here, has been sent to the agency and is available on the AASLD website (<http://www.aasld.org>).

The options under consideration fall into three categories:

1. improving package labels
2. limiting large volume sales (smaller package sizes, and/or blister packaging), and
3. unbundling or adjustment of dosage within narcotic compounds.

Improvement in Package Labeling

Revised package labeling is part of the Proposed Amendment by FDA published in December 2006, but does not go far enough. FDA asked for additional information on limiting package size and other strategies, but repeatedly affirms that the widespread usage of over-the-counter (OTC) products containing acetaminophen or NSAIDs, confirms that they are generally both safe and effective in the proper dosages. Package labeling and patient education may impact some people but the substance user who impulsively overdoses inadvertently or the teenage suicide will be unaffected by these changes. The Proposed Amendment does state that the word acet-

aminophen should be present and highlighted in some fashion (e.g., fluorescent ink) on the front of all packages (the product display panel or PDP). Currently, compounds such as Theraflu[®] or Tylenol PM[®] are not required to list all ingredients on the PDP, the most visible site for consumers. Warnings suggested by FDA will be somewhat more explicit concerning the risk of overdosing, suggesting that “severe liver damage” may occur if repeated doses are taken, and giving a specific caution about taking more than one acetaminophen containing preparation. To date, nothing is specifically stated regarding patients with chronic liver disease, fasting, alcoholics or those taking medications known to interact with acetaminophen or repeated daily dosing at the limit of 4 gms. Some data have been forthcoming confirming that therapeutic acetaminophen in other liver diseases such as acute viral hepatitis is associated with a higher probability of acute liver failure.^{23,24} It is unlikely that definitive research data will ever be provided that will implicate 4 grams per day as too high for the average patient, in part because such studies are impossible to perform. However, the fact that even 10% of acetaminophen related ALF occurs in the setting of therapeutic doses of 2-4 gm suggests that some harm reduction would be accomplished by limiting daily dosing for alcoholics to 2 gms/day. While the data are limited that reduced dosing will effect an improvement in outcomes, acetaminophen is a dose-related toxin. It makes intuitive sense that we advise caution to patients who have any of these ongoing issues since they may experience a combined toxic effect.

AASLD has now recommended consideration of the following more explicit labeling:

- This product can cause severe or even fatal liver injury. The chance is higher if you:
 - Use this drug at the maximum recommended dose (4 grams/day) for 5 or more consecutive days,
 - Use this drug simultaneously with other drugs containing acetaminophen
 - Use this drug simultaneously with certain prescription medications (isoniazid, phenobarbital, warfarin)
 - Use this drug at the maximum recommended dose (4 grams/day) when food intake is restricted or prohibited
 - Use more than 2 grams/day of this drug while drinking alcohol
 - Have an ongoing serious liver condition

Limiting Package Size

Given the limited scope of the 2002 NDAC meeting and the continued increasing problem of acetaminophen poisoning, we asked FDA to explore these additional issues not touched upon previously. AASLD has called for another NDAC meeting to discuss how best to tackle the

ongoing impulsive behavior in suicides and in patients with pain that leads to so many needless hospital admissions and fatalities. Consideration at such a meeting should be given to limiting the number of tablets in bottles of acetaminophen and introduction of blister packaging to protect the patient from the harmful effects of the product based on the experience in the United Kingdom. While these are indirect methods short of removing the drug from the market, they would send a strong signal that FDA takes the problem seriously and would like to limit these dangerous practices. This does not limit in any way the ability of a patient to obtain acetaminophen for therapeutic use, but serves as a deterrent for the casual or unknowing overdose patient. AASLD has provided an opinion that “*reducing package size and changing package configuration (to blister packs) has the potential to significantly reduce the number of cases of acetaminophen hepatotoxicity in the U.S.*”

Unbundling or Limiting Acetaminophen in Narcotic Preparations

This final step is a complicated one not directly addressed in the FDA’s Proposed Amendment. Currently, narcotic-acetaminophen compounds are the only narcotics that can be dispensed in most states without a triplicate narcotic prescription form. This concession to physician’s convenience (few of us keep triplicates close at hand) has led to their widespread use for short- and long-term pain control. Since acetaminophen is a weak pain reliever and scant data suggesting synergy with narcotics exists, the value of repeated acetaminophen exposure in the setting of moderate or severe pain should be questioned. There is no good evidence that “more is better” or faster in providing pain relief. AASLD has in this instance recommended *discussion about revising and possibly restricting the use of OTC and prescription narcotic-acetaminophen preparations*. Short of total unbundling, smaller quantities of acetaminophen (325 mg instead of 500 or 750 mg) within the combination tablet might be a safer option for the addicted patient. Since narcotic/acetaminophen compounds can be purchased readily over the Internet using offshore sites, there is currently no restriction on availability of these preparations. No prescription is required to obtain the drugs via at least some websites that purport to provide their own prescribing doctors. How unbundling or the limitation of acetaminophen in a compound to 325 mg could be accomplished remains to be seen, unless all combinations or at least those with 500 mg or 750 mg per tablet were banned completely. Separating acetaminophen entirely from the narcotic might be difficult initially but would likely be easier for FDA to oversee in the long run.

Conclusions

Most hepatologists are all too aware of acetaminophen poisonings as a common and not so trivial part of our practice. Publicity in recent years has led the better-informed and more cautious segment of the population to limit its use at least in terms of the amounts taken per day. Nonetheless, more detailed studies of the nature of the unintentional overdose are needed to delineate how we could better arrest this alarming trend. Cases of attempted suicide that do not arrive at hospital in a timely fashion represent an additional needless risk. More needs to be done to put concrete proposals for harm reduction on the table. The AASLD's initial response is a bold first step. Further consultation by AASLD and other interested groups with FDA and with the White House Office on Narcotic Drug Control Policy or the Bureau of Alcohol, Tobacco and Firearms and other agencies that oversee narcotic regulation are in order to bring about better outcomes in this highly vulnerable patient group.

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